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and to enhanced proximal tubular reabsorption**

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Salt Sensitivity in Humans Is Linked to Enhanced Sympathetic Responsiveness and to Enhanced Proximal Tubular Reabsorption

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SUMMARY If high sodium intake is involved in the pathogenesis of essential hypertension, the effects of changing the sodium intake should be demonstrable in the susceptible part of the normotensive population. Therefore, we have investigated the effects of moderate salt restriction in 52 young normotensive subjects with and without a family history of hypertension; 22 (42%) responded to moderate salt restriction (200 to 50 mmol/day) over 2 weeks, with a significant fall in blood pressure shown by continuous automatic blood pressure recordings. Accordingly, these subjects were classified as salt-sensitive, and the remainder as salt-resistant. Compared to salt-resistant subjects, salt-sensitive subjects showed a 2.5-fold higher incidence of a positive family history of hypertension ($p < 0.01$), and a significantly higher blood pressure and lower salivary sodium concentration during the usual high sodium diet. Although there were no differences in Na,K-ATPase activity and in Na-K cotransport of erythrocytes, the pressor response to infused norepinephrine in salt-sensitive subjects was double that of salt-resistant subjects independent of the diet and this was linked to indirect evidence for enhanced proximal tubular sodium reabsorption. On the usual high sodium diet, 40% of the normal population may be salt-sensitive and prone to develop hypertension. Hypersensitivity to catecholamines (genetically determined?) may be the cause of salt sensitivity. A low sodium concentration in saliva deserves further study as a simple screening test to identify salt-sensitive subjects. (Hypertension 6: 152-158, 1984)

KEY WORDS • hypertension • salt sensitivity • sympathetic hyperresponsiveness • genetics • proximal tubular sodium reabsorption

ALTHOUGH hypertensive subjects respond to salt restriction with a decrease in blood pressure,¹⁻⁷ it is generally held that normotensive subjects do not respond to restriction of the usual daily sodium intake of between 10 and 20 g.⁷⁻¹⁰ This implies that normotensive subjects cannot become hypertensive because of a high sodium intake. By continuous automatic blood pressure recordings over several hours in a small group of young normotensive sub-

jects, we had previously demonstrated a significant fall in blood pressure in about half the subjects after a moderate reduction of sodium intake from 200 to 50 mmol/day. We therefore proposed that these subjects were prone to develop hypertension in later life on their usual high sodium intake.¹¹

In our present study, we have confirmed in a large group of healthy young subjects that salt-sensitive normotensive subjects exist and that salt sensitivity is linked to enhanced sympathetic responsiveness.¹²

Material and Methods

We studied 52 normotensive male medical students, aged 20 to 25 years both on their usual daily diet containing 200 mmol of sodium and 80 mmol of potassium, and after 2 weeks on a daily diet containing 50 mmol of sodium and an unchanged potassium and caloric intake. The sequence of the diets was randomized. The amount of sodium and potassium was that usually consumed in the usual diet in Western Europe. The low sodium diets were provided by the dietetic

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department of the hospital: moderate salt restriction was achieved by eliminating food containing added salt and by not using salt for cooking and baking except for bread. The subjects received the diet in the hospitals but were not kept on a metabolic ward.

Protocol

After a 24-hour urine specimen had been collected, a needle was placed in a forearm vein of the fasting subject at 8:00 am. The subject then rested supine for 90 minutes, after which blood was taken for determination of plasma renin, aldosterone, norepinephrine, epinephrine, plasma creatinine, electrolytes, and Na,K-ATPase activity and Na-K cotransport in erythrocytes. During this time, pulse rate and systolic, diastolic, and mean blood pressures were recorded every minute using a Dinamap Model 845 with recorder 950 (Applied Medical Research Corporation, Tampa, Florida). Also during this time, about 3 to 5 ml of spontaneous saliva was collected. At 3 hours after blood collection, in vivo mineralocorticoid activity was measured by subtraction potential difference¹³ to relate it to concurrent plasma aldosterone levels. On the same day after 30 minutes of supine bed rest, the subjects also received a graded infusion of norepinephrine (0.1, 0.2, and 0.4 $\mu\text{g}/\text{kg}/\text{min}$), each over 5 minutes, while blood pressure and pulse rate were recorded every minute.

The family history of hypertension was evaluated by questionnaire administered to each subject and given to the family doctor. Those with established hypertension in parents or grandparents were considered positive; those with normotensive parents and grandparents, negative. The subjects were also tissue-typed for HLA-antigens.

Measurements

Methods of hormone measurements were: plasma renin by the method of Boyd et al.,¹⁴ aldosterone by the method of Ito et al.,¹⁵ and catecholamines by the method of Hörtnagl et al.¹⁶ Blood pressures and pulse rates used for comparison of the effects of the diets were the means of values recorded during the resting period. Due to the large number of measurements ($n > 90$), intraindividual changes could be calculated for each subject by the unpaired t test. Pressor response to infused norepinephrine was assessed as reported previously.¹¹

For the measurement of Na,K-ATPase and of cotransport, 250 μl erythrocytes were washed twice in physiological saline and were incubated in triplicate at 37°C for 1 hour with 150,000 cpm of ⁸⁶Rb in 0.5 ml of a medium with or without 1.0×10^{-4} mol of ouabain or 1.0×10^{-4} mol of ouabain and 1.07 mmol of furosemide. The medium contained sodium, potassium, calcium, magnesium, chloride, phosphate, and glucose in concentrations of 145, 3.9, 1.50, 0.50, 140, 1.36, and 11.1 mmol/liter, respectively. Na,K-ATPase and cotransport were calculated from the difference of ⁸⁶Rb uptake in the presence of ouabain and in the presence of ouabain and furosemide, respective-

ly. Statistical methods were: the Wilcoxon matched pairs signed rank test, Student's paired and unpaired t test, the sign test of Dixon and Mood, and the u-test of Mann-Whitney.

Results

A low sodium diet reduced systolic, diastolic, and mean blood pressure levels significantly by more than 3 mm Hg in 22 of 52 individuals, as shown by the mean of at least 90 blood pressure measurements per subject per diet. The standard error of the mean for a single 90-minute period ranged between 0.42 and 0.84 mm Hg. Another study performed by us (Skrabal et al., unpublished data) has shown that, without intervention, mean blood pressure is reproducible within 2 mm Hg for the same subject even many weeks apart. The frequency distribution of change of blood pressure during the low sodium diet is shown in Figure 1. As calculated by the signed rank test of Dixon and Mood and the Wilcoxon test, the observed distribution of

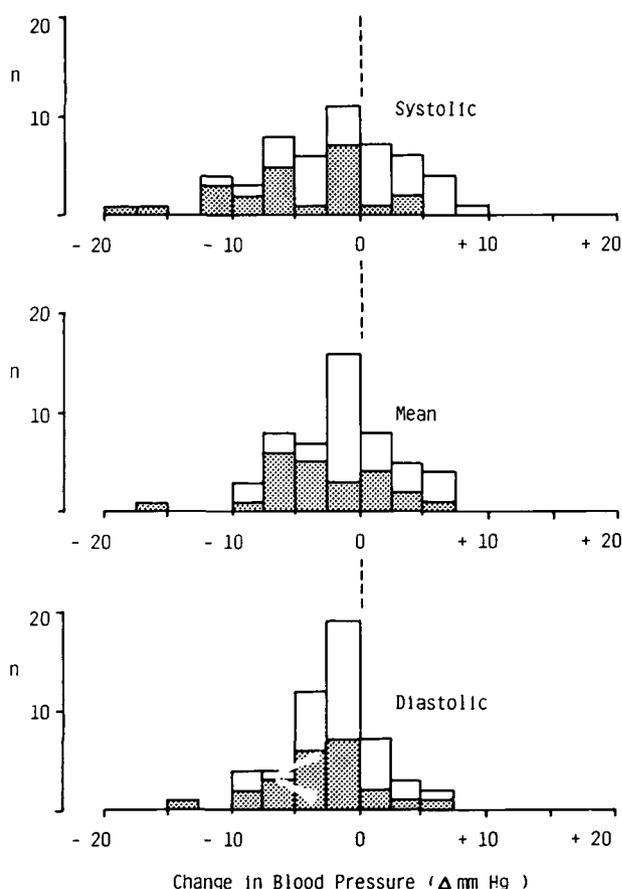


FIGURE 1. Frequency distribution of change of blood pressure during the low sodium diet. The observed distribution of change of systolic, diastolic, and mean blood pressure did not correspond to a binomial distribution (Wilcoxon matched pairs signed rank test for diastolic blood pressure, $p < 0.001$). The shaded bars indicate subjects with a positive family history of hypertension.

changes in systolic, diastolic, and mean blood pressure does not correspond to a binomial distribution: blood pressure rose in 17 subjects and fell in 35. Consequently, the group was dichotomized, and the 22 subjects who showed intraindividual significant decreases of blood pressure of more than 3 mm Hg were classified as salt-sensitive and the remainder as salt-resistant.

As shown in Table 1, salt-sensitive and salt-resistant subjects lost a similar amount of weight when changed from the usual to the low sodium diet, and there were no significant differences in plasma and urinary catecholamines. Uric acid also increased significantly in both groups, but the increase in the salt-sensitive group was twice as high as in the salt-resistant group. Concomitantly, uric acid clearance and fractional uric acid excretion decreased to half its initial value in salt-sensitive subjects ($p < 0.001$) during sodium restriction, but remained unchanged in salt-resistant subjects (Figure 2). Furthermore, although plasma renin and aldosterone levels were identical during the high sodium diet in both groups, salt-resistant subjects had a markedly more stimulated renin-aldosterone axis during the low sodium diet (Figure 3). The semilogarithmic regression of plasma aldosterone to in vivo mineralocorticoid activity gave the following regression equations: for salt-sensitive subjects, the subtraction PD (mV) = 51.9 log PA (ng/dl) - 39.8, $r = 0.71$, $n = 26$, $p < 0.001$; for salt-resistant subjects, the sub-

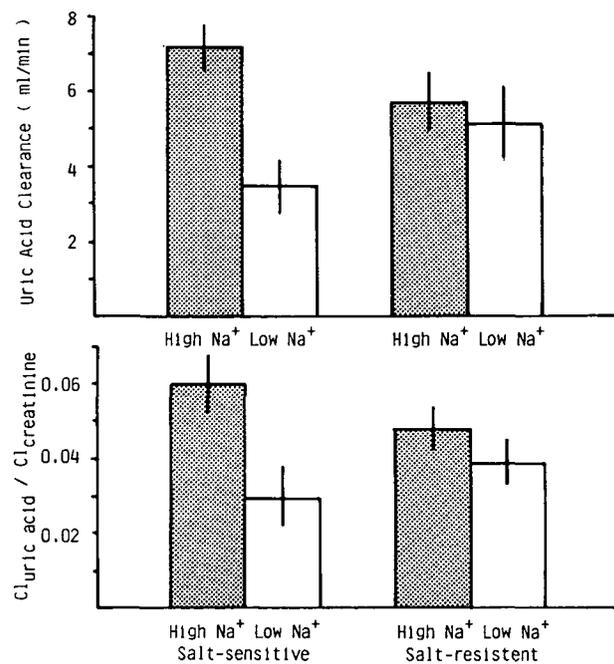


FIGURE 2. Uric acid clearance and fractional uric acid excretion in salt-sensitive and salt-resistant subjects at high and low levels of sodium intake (mean \pm SEM). Only in salt-sensitive subjects did uric acid clearance and fractional uric acid excretion fall significantly ($p < 0.001$) to half their initial value, whereas it remained unchanged in salt-resistant subjects.

TABLE 1. Blood Pressure Values and Biochemical Data in Salt-Sensitive and Salt-Resistant Subjects During High and Low Sodium Intakes (Mean \pm SEM)

	Salt-sensitive subjects (n = 22)		Salt-resistant subjects (n = 30)	
	High salt diet	Low salt diet	High salt diet	Low salt diet
Body weight (kg)	76.2 \pm 2.45	\dagger -0.86 \pm 0.247	76.8 \pm 2.05	\ddagger -0.64 \pm 0.143
Systolic blood pressure (mm Hg)	<u>125.1</u> \pm 1.59	117.4 \pm 1.94	<u>117.1</u> \pm 1.46	118.5 \pm 1.63
Diastolic blood pressure (mm Hg)	<u>65.7</u> \pm 1.56	61.1 \pm 1.73	<u>61.8</u> \pm 1.14	62.6 \pm 1.24
Mean blood pressure (mm Hg)	<u>86.1</u> \pm 1.36	81.0 \pm 1.57	<u>80.9</u> \pm 1.08	82.3 \pm 1.23
Pulse rate (bpm)	70.8 \pm 1.42	69.3 \pm 2.02	66.6 \pm 1.95	69.6 \pm 2.37
24-hr urinary sodium (mmol)	203.5 \pm 12.97	\ddagger 37.4 \pm 3.31	177.9 \pm 15.79	\ddagger 40.6 \pm 5.66
24-hr urinary sodium/creatinine ratio (mmol/g)	121.9 \pm 7.71	\ddagger 20.7 \pm 1.69	106.7 \pm 7.19	\ddagger 22.3 \pm 3.07
24-hr urinary potassium (mmol)	70.0 \pm 4.29	84.2 \pm 10.12	69.1 \pm 3.91	* 91.6 \pm 7.47
24-hr urinary potassium (creatinine ratio) (mmol/g)	41.3 \pm 1.97	52.0 \pm 8.33	41.8 \pm 1.93	* 51.6 \pm 4.76
Serum sodium (mmol/liter)	138.3 \pm 0.86	141.9 \pm 1.10	140.1 \pm 0.57	140.9 \pm 0.95
Serum potassium (mmol/liter)	4.20 \pm 0.116	4.29 \pm 0.115	4.37 \pm 0.089	4.39 \pm 0.09
Serum creatinine (mg/dl)	1.00 \pm 0.033	1.07 \pm 0.040	1.00 \pm 0.032	1.02 \pm 0.038
Uric acid (mg/dl)	5.67 \pm 0.261	\dagger <u>6.97</u> \pm 0.336	* 5.94 \pm 0.193	* <u>6.59</u> \pm 0.202
Plasma renin activity (pg/ml/hr)	337.7 \pm 52.2	\dagger <u>573.4</u> \pm 79.1	* 350.1 \pm 34.10	\ddagger <u>1042.7</u> \pm 175.6
Plasma aldosterone (ng/dl)	7.2 \pm 1.01	\ddagger 21.6 \pm 2.39	8.8 \pm 0.62	\ddagger 35.8 \pm 7.84
Plasma norepinephrine (ng/ml)	0.296 \pm 0.038	0.250 \pm 0.015	0.242 \pm 0.021	0.270 \pm 0.029
Plasma epinephrine (ng/ml)	0.066 \pm 0.013	0.064 \pm 0.017	0.039 \pm 0.006	0.062 \pm 0.016
Urinary aldosterone (μ g/24 hr)	6.5 \pm 0.97	\ddagger <u>15.0</u> \pm 1.44	\dagger 7.6 \pm 1.17	\ddagger <u>28.8</u> \pm 3.80
Urinary norepinephrine (μ g/24 hr)	50.1 \pm 8.50	42.6 \pm 3.67	47.6 \pm 4.10	46.9 \pm 6.30
Urinary epinephrine (μ g/24 hr)	11.9 \pm 1.13	14.6 \pm 1.30	17.5 \pm 4.24	18.5 \pm 3.69

Differences between the groups: * $p < 0.05$; $\dagger p < 0.01$; $\ddagger p < 0.001$.

The differences between salt-sensitive and salt-resistant subjects are underlined.

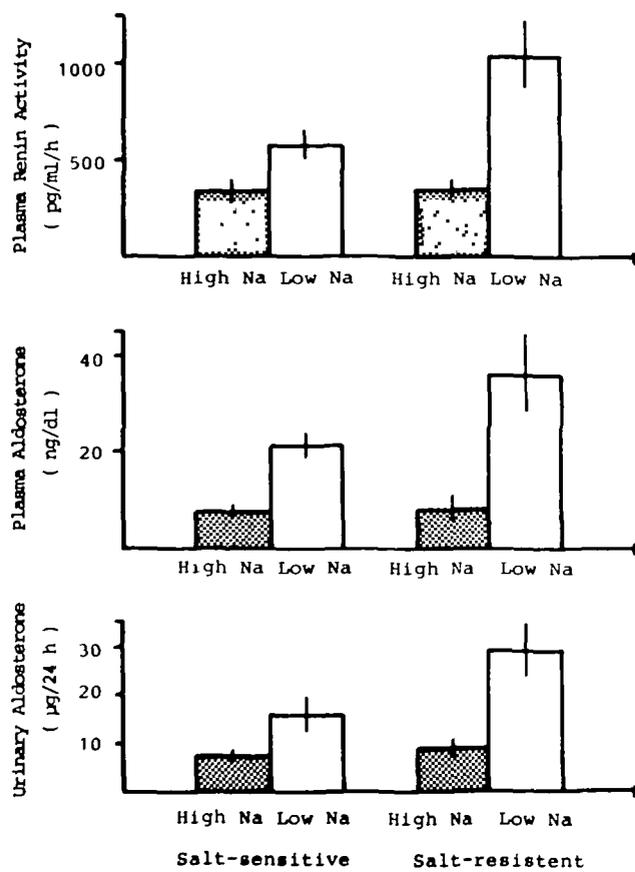


FIGURE 3. Plasma renin activity and plasma and urinary aldosterone levels in salt-sensitive and salt-resistant subjects at high and low levels of sodium intake (mean ± SEM).

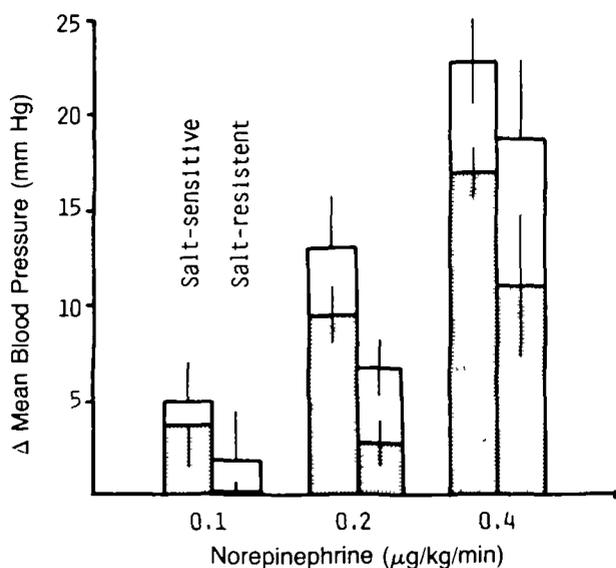


FIGURE 4. Increase of mean blood pressure at 0.1, 0.2, and 0.4 µg/kg/min norepinephrine in salt-sensitive and salt-resistant subjects during high and low levels of sodium intake (mean ± SEM). Student's unpaired t test between salt-sensitive and salt-resistant subjects ($p < 0.01$) and Mann Whitney u-test ($p < 0.005$). Total height of bars—pressor response during high sodium diet. Shaded bars—pressor response during low sodium diet.

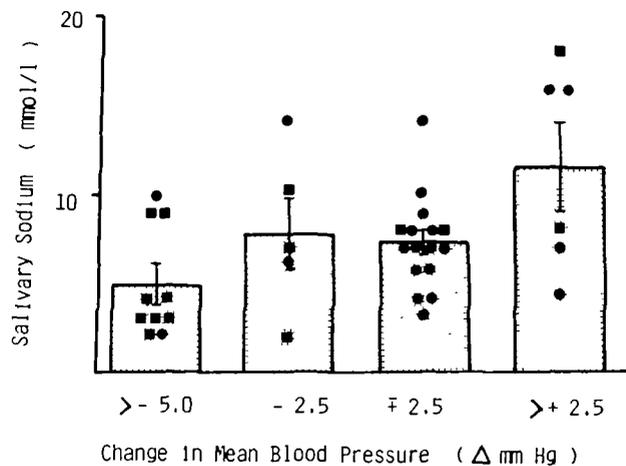


FIGURE 5. Relationship of salivary sodium concentration to change in blood pressure when subjects were changed from high to low sodium intake (mean ± SEM). ($r = -0.41$; $p < 0.05$, $n = 37$). Subjects with (■) and without (●) a family history of hypertension.

traction PD (mV) = 31.7 log PA (ng/dl) - 12.6, $r = 0.52$, $n = 24$, $p < 0.01$. The slopes were not significantly different. Salt-sensitive subjects had similar blood pressure values during the low sodium diet, but had significantly higher blood pressure during the usual high sodium diet (Table 1).

The increase in mean blood pressure during the norepinephrine infusion in both groups is shown in Figure 4. As can be seen, the increase in blood pressure during norepinephrine infusion in salt-sensitive subjects is nearly double that of salt-resistant subjects at all rates of infusion, and this difference also persists when the subjects were put on a low sodium diet. Figure 5 shows that subjects with the most marked decrease of blood pressure during the low sodium diet had also the lowest salivary sodium concentration and vice versa. The incidence of a positive family history of hypertension in salt-sensitive subjects was 15 of 22 (68.2%) and eight of 30 (26.7%) in salt-resistant subjects ($\chi^2 = 8.9$, $p < 0.01$). Furthermore, the distribution of certain HLA-antigens shows remarkably different trends (Table 2).

TABLE 2. Frequency of the HLA-Loci in Salt-Sensitive and Salt-Resistant Subjects

HLA Locus	Salt-sensitive subjects (n = 32)		Salt-resistant subjects (n = 32)		Total incidence (%)
	No.	Incidence (%)	No.	Incidence (%)	
A 3	4 (4)	12.5 (18.2)	9 (7)	28.1 (29.2)	20.3 (23.9)
A 19	5 (4)	15.6 (18.2)	1 (0)	3.1 (0)	9.4 (8.7)
B 13	5 (4)	15.6 (18.2)	1 (1)	3.1 (4.2)	9.4 (10.9)
B 27	5 (5)	15.6 (22.7)	1 (1)	3.1 (4.2)	9.4 (13.0)

Data are from 22 salt-sensitive and 24 salt-resistant normotensive subjects, and also from 18 patients with borderline hypertension, age range 20 to 35 years, which were also classified into salt-sensitive ($n = 10$) and salt-resistant subjects ($n = 8$). The figures for normotensive subjects alone are given in parenthesis.

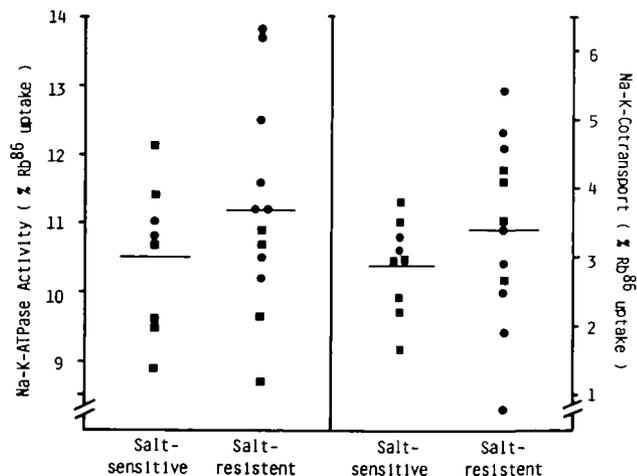


FIGURE 6. *Na,K-ATPase* activity and *Na-K* cotransport (expressed as ouabain-sensitive and furosemide-sensitive ⁸⁶Rb uptake) in salt-sensitive and salt-resistant subjects. Subjects with (■) and without (●) a family history of hypertension.

Figure 6 demonstrates that there are no significant differences in *Na,K-ATPase* activity and cotransport between salt-sensitive and salt-resistant subjects.

Discussion

If a high sodium intake is of relevance in the pathogenesis of hypertension, great interindividual differences in salt sensitivity must exist, since only a small part of the population develops hypertension during a high sodium intake. Consequently, it should be possible to identify the salt-sensitive individuals in the prehypertensive state. Therefore, we have studied normotensive subjects with and without a family history of hypertension, a proportion of whom will certainly develop hypertension in later life. Although others did not show a fall of blood pressure after sodium restriction from casual blood pressure readings, we have shown an intraindividually significant fall of blood pressure in 42% of normotensive subjects whom we classified as salt-sensitive by continuous automatic blood pressure recordings over several hours.

Although the mean value recorded during this resting period gives apparently a very good index of the 24-hour blood pressure profile,¹⁷ some of the blood pressure changes observed may still be random and may be due to factors hardly controllable such as different levels of personal emotional stress (e.g., due to events concerned with the medical curriculum), so that we may have misclassified some of the subjects. The biochemical and other differences observed in the two groups are therefore even more remarkable. Since a positive family history of hypertension was nearly three times more frequent in the salt-sensitive group than in the salt-resistant group, we conclude that the

phenomenon of salt sensitivity may be inherited. The varying incidence of certain HLA-antigens (Table 2) is also suggestive for a genetic basis of this observation. Due to the low overall incidence of the different loci, an even larger study is needed to confirm the presently observed trends. The significantly higher systolic, diastolic, and mean blood pressure levels in the salt-sensitive group on the usual high sodium intake suggest that some of these subjects may already be slowly developing hypertension, if they continue their usual high sodium intake.

What could be the biochemical basis of this observed difference of salt sensitivity? Since both groups excreted the amount of sodium given in the diet after 2 weeks on the low sodium diet, we can safely assume that both groups are in a steady state of sodium balance. Since the subjects received and consumed the sodium-restricted diet from the dietetic department of the hospital, we consider a single determination of urinary sodium excretion as adequate control, especially since completeness of the collection was ensured by the measurement of urinary creatinine excretions (Table 1). Both groups also lost a similar amount of weight (and presumably body water) during reduction of sodium intake; apparently, salt-sensitive subjects do not retain appreciably more sodium during the high sodium intake. However, it is remarkable that, in salt-resistant subjects, the renin-aldosterone axis had to be stimulated nearly twice as much to achieve sodium balance during the low sodium diet (Figure 3). This corresponds to observations made by Kawasaki et al.³ and Fujita et al.⁴ in salt-resistant hypertensive subjects. Our interpretation of this finding is that salt-sensitive subjects have more effective mechanisms with which to maintain sodium balance at low levels of sodium intake and therefore need a less stimulated renin-aldosterone axis. A genetically determined enhanced sensitivity of aldosterone receptors would have been an attractive hypothesis, but the relationship between aldosterone levels in plasma and *in vivo* mineralocorticoid activity at the cellular level was not statistically different in both groups.

The other important difference observed between salt-sensitive and salt-resistant subjects was the markedly enhanced blood pressure responsiveness to infused norepinephrine (Figure 4). This difference between the salt-sensitive and the salt-resistant subjects persisted at high and low levels of sodium intake and was not due to different levels of plasma and urinary catecholamines (Table 1). We have also confirmed our and other previous observations^{11, 18} that salt restriction lowers the pressure response to infused norepinephrine. It is remarkable that in our study moderate sodium restriction from 200 to 50 mmol/day did not raise plasma and urinary catecholamines, as is seen with more extreme variations of sodium intake^{9, 18} and that plasma catecholamine levels in salt-sensitive and salt-resistant normotensive subjects were not different, which is in contrast to the results of Fujita et al.⁴ and Campese et al.⁷ in hypertensive subjects. Unfortunately, we were unable to determine plasma concentration

of norepinephrine during the graded infusion, so that it is uncertain whether salt-sensitive and salt-resistant subjects achieved comparable blood levels of norepinephrine. It would have been important to measure norepinephrine levels during the infusion since Dietz and Coworkers¹⁹ have demonstrated that stroke-prone SHR rats may have a defect in norepinephrine uptake during salt loading. It is also important to consider the work of Polgar *et al.*,²⁰ who performed norepinephrine infusions in normal subjects and observed that hyperreactors responded to acute hypertonic saline infusions with a natriuresis in a fashion similar to patients with stable essential hypertension.

We believe that enhanced sympathetic responsiveness may be the cause of salt sensitivity. Low level stimulation of renal nerves is known to cause proximal sodium reabsorption without changing renal blood flow or renal resistance and this effect is blocked by phentolamine.^{21–22} With the same level of sympathetic stimulation in salt-sensitive and salt-resistant subjects (as indicated by similar plasma and urinary catecholamines), an increased sensitivity to norepinephrine in salt-sensitive subjects would lead to enhanced sodium reabsorption at the proximal tubules, so that a less stimulated renin-aldosterone axis at the low level of sodium intake (Figure 3) would still guarantee adequate overall sodium reabsorption. Evidence for an enhanced proximal tubular salt and volume reabsorption in the salt-sensitive group is also the enhanced uric acid reabsorption,^{23,24} as indicated by the twofold higher rise of plasma uric acid and fall of uric acid clearance in this group (Figure 2). At the high level of sodium intake, however, salt-sensitive subjects should also suppress their renin-aldosterone axis more than salt-resistant subjects in order to counter-balance the effects of enhanced sympathetic responsiveness. But, as shown in Figure 3, salt-sensitive subjects are unable to suppress their renin-aldosterone axis more than salt-resistant subjects; obviously, both systems are already completely suppressed and outside their regulatory range.^{25–26} Consequently, in salt-sensitive subjects, blood pressure rises and sodium balance is achieved by pressure natriuresis.²⁷ A generalized enhanced sympathetic responsiveness in salt-sensitive subjects would also decrease the volume of the vascular bed (e.g., as seen in pheochromocytoma). Therefore, if we assume that salt-sensitive subjects are those prone to develop hypertension in later life, enhanced sympathetic responsiveness would explain why, at the beginning of hypertension, contraction of the intravascular volume and not expansion is found^{28,29} (although this contraction may still be associated with a relative fluid overload for the given capacity of the vascular bed).

If our concept is correct, why is blood pressure not higher in salt-sensitive than in salt-resistant subjects during the low sodium intake, considering that they have similar levels of plasma norepinephrine but increased vascular response? One possible explanation is that plasma renin activity (and probably also circulating angiotensin II) in salt-sensitive subjects on average is only half that of salt-resistant subjects (Table 1).

How does the currently favored hypothesis of an excess of a ouabain-like natriuretic hormone or of a generalized sodium transport defect fit into our concept? Since both cardiac glycosides and a raised intracellular sodium concentration are known to enhance the response of blood vessels to sympathetic stimulation,^{30,31} either mechanism may have mediated the enhanced pressor response to infused norepinephrine in the salt-sensitive group. However, in two different bioassays and in a sensitive digoxin-radioimmunoassay, we were unable to detect a sodium transport inhibitor in any of the groups at any level of sodium intake (unpublished data). Furthermore, Na,K-ATPase activity and Na-K cotransport of erythrocytes were not different in salt-sensitive and salt-resistant subjects (Figure 6). Alternatively, differences in the number or affinity of alpha-adrenoreceptors, or in the relation between alpha- and beta-receptors, or in norepinephrine release, uptake, or metabolism may exist between salt-sensitive and salt-resistant subjects. These differences may be inherited or imprinted later by different psychological and physiological responses to stress.³²

We do not suggest that salt sensitivity is a qualitative phenomenon. Rather, it appears to be a quantitative phenomenon, with those who are most sensitive responding with the most marked change of blood pressure. Therefore, the chosen cutoff point for dichotomizing the individuals has been of minor importance, and other cutoff points have provided similar results (see, for example, Figure 5). Reducing sodium intake to a level where at the distal tubules a less stimulated renin-aldosterone axis can counterbalance the effects of enhanced sympathetic responsiveness on proximal tubular sodium reabsorption could be a measure to prevent the development of hypertension in the salt-sensitive portion of the population. A low sodium concentration in spontaneous saliva, which is also compatible with the effects of enhanced sympathetic stimulation of the salivary gland,³³ deserves further study as a possible simple marker for salt sensitivity.

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References

- 1 Dahl LK. Salt and hypertension. *Am J Clin Nutr* 1972;22:231–244
- 2 Tobian L. Salt and hypertension. In: Perry HM, Smith WM, eds. *Mild hypertension: to treat or not to treat*. New York: New York Academy of Science, 1978:178–197
- 3 Kawasaki T, Delea CS, Bartter FC *et al.* The effect of high-sodium and low sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* 1978;64:193–198
- 4 Fujita T, Henry WL, Bartter FC *et al.* Factors influencing blood pressure in salt-sensitive patients with hypertension. *Am J Med* 1980;69:334–344

5. Sullivan JM, Ratts TE, Taylor C et al. Hemodynamic effects of dietary sodium in man: a preliminary report. *Hypertension* 1980;2:506-514
6. Longworth DL, Drayer JIM, Weber MA et al. Divergent blood pressure responses during short-term sodium restriction in hypertension. *Clin Pharm Therap* 1980;27:544-546
7. Campese VM, Romoff MS, Levitan D et al. Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. *Kidney Int* 1982;21:371-376
8. Romoff MS, Keusch G, Campese VM et al. Effect of sodium intake on plasma catecholamines in normal subjects. *J Clin Endocrinol Metab* 1979;48:26-31
9. Luft FC, Rankin LI, Henry DP et al. Plasma and urinary norepinephrine values at extremes of sodium intake in normal man. *Hypertension* 1979;1:261-266
10. Burstyn P, Homall DEE, Watchorn C. Sodium and potassium intake and blood pressure. *Br Med J* 1980;281:537-539
11. Skrabal F, Auböck J, Hörtnagl H. Low sodium/high potassium diet for prevention of hypertension: probable mechanisms of action. *Lancet* 1981;2:895-900
12. Skrabal F, Herholz H, Neumayer M, Hörtnagl H, Schönitzer D. Salzsensitivität beim Menschen als Folge erhöhter sympathischer Empfindlichkeit. *Therapie woche* 1982;32: 5748
13. Skrabal F, Auböck J, Edwards CRW et al. Subtraction potential difference. *in vivo* assay for mineralocorticoid activity. *Lancet* 1978;1:298-302
14. Boyd GW, Adamson AR, Fitz AE. Radioimmunoassay determination of plasma renin activity. *Lancet* 1966;1:213-218
15. Ito T, Woo J, Haning R. A radioimmunoassay for aldosterone in human peripheral plasma including a comparison of alternate techniques. *J Clin Endocr* 1972;34:106-112
16. Hörtnagl H, Benedict CR, Grahame Smith DG. A sensitive radioenzymatic method for adrenaline and noradrenaline in plasma. *Br J Clin Pharmacol* 1977;4:533-538
17. Weber MA, Drayer J, Wyle FA, Brewer DD. Representative value for whole day BP monitoring. *J Am Med Assoc* 1982;248:1626-1628
18. Rankin LI, Luft FC, Henry DP, Gibbs PS, Weinberger MH. Sodium intake alters the effects of norepinephrine on blood pressure. *Hypertension* 1981;3:650-656
19. Dietz R, Schomig A, Rascher W, Strasser R, Kubler W. Enhanced sympathetic activity caused by salt loading in spontaneously hypertensive rats. *Clin Sci* 1980;59:171-177
20. Polgár E, Kanyár B, Somorjai F, Komor K. Sodium excretion after saline infusion under normal conditions and in the successive stages of hypertensive disease. *Acta Med Acad Sci Hungaricae* 1973;30:311-318
21. Zambraski EJ, Dibona GF, Kaloyanides GJ. Specificity of neural effect on renal tubular sodium reabsorption. *Proc Soc Exp Biol Med* 1976;151:543-546
22. Dibona GF. Neurogenic regulation of renal tubular sodium reabsorption. *Am J Physiol* 1977;233:F73-F81
23. Greger R, Lang F, Deetjen P. Urate handling by the rat kidney IV. Reabsorption in the loops of Henle. *Pflüger Arch* 1974;352:115-120
24. Senckjian HO, Knight TF, Sansom SC, Weinman EJ. Effect of flow rate and the extracellular fluid volume on proximal urate and water absorption. *Kidney Int* 1980;17:155-161
25. Skrabal F. Aldosterone and *in vivo* mineralocorticoid activity in normotensive and hypertensive man. *J Roy Soc Med* 1979;72:252-259
26. Skrabal F. Nomogramm zur Schätzung der Plasminreninaktivität anhand des Natrium-Kreatinin-Quotienten im Spontanharn. *Dtsch med Wschr.* 1975;100:2649-2651
27. Borst JGG, Borst-De Geus A. Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1963;1:768-782
28. Tarazi RC, Frohlich ED, Dustan HP. Plasma volume in men with essential hypertension. *N Eng J Med* 1968;278:762-765
29. Bauer JH, Brooks CS. Body-fluid composition in normal and hypertensive man. *Clin Sci* 1982;62:43-49
30. Leonard E. Alteration of contractile responses of artery strips by a potassiumfree solution, cardiac glycosides and changes in stimulation frequency. *Am J Physiol* 1957;189:185-190
31. Hermesmeyer K. Electrogenesis of increased norepinephrine sensitivity of arterial vascular muscle in hypertension. *Circ Res* 1976;38:362-367
32. Glass DC. Psychological and physiological responses of individuals displaying type A behaviour. *Acta Med Scand* 1982; 660 (Suppl):193-202
33. Schneyer LH, Thavornthong T. Isoproterenol induced stimulation of sodium reabsorption in perfused salivary duct. *Am J Physiol* 1973;224:136-139